REMARKS

Claims 1-54 are pending in this application and presented for examination. Applicants hereby elect Group II, drawn to a method for identifying an intact charge-switch NP probe and to an intact charge-switch NP probe, with traverse. Claims readable thereon include claims 18-44. The claims as pending are attached for the Examiner's convenience. Reconsideration of the restriction requirement is respectfully requested.

Applicants traverse the restriction requirement as the two criteria for a proper restriction requirement have not been met. Under M.P.E.P. § 803, to be proper, the inventions must be independent or distinct; and there must be a serious burden on the Examiner.

Applicants believe Groups I and II should be joined and claims 1-44 examined on their merits. Both independent claims 1 and 18 set forth a sample comprising an intact charge-switch NP probe, an enzyme and an energy field such as an electric field. As such, the requirements for a proper restriction between these two groups has not been met. Accordingly, Groups I and II should be joined and examined together.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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PENDING CLAIMS

1. A method for separating an intact NP probe from a phosphate detectable moiety, said method comprising:

a) providing a sample comprising an intact NP probe with a detectable moiety attached thereto, whereupon an enzymatic cleavage of said intact NP probe, which produces a phosphate detectable moiety, said phosphate detectable moiety carries a molecular charge which is different than the molecular charge of said intact NP probe; and

b) applying an energy field to said sample, thereby separating said phosphate detectable moiety from said intact NP probe.

2. The method according to claim 1, wherein said intact NP probe is a charge-switch nucleotide phosphate probe having a detectable moiety on a terminal phosphate.

3. The method according to claim 2, wherein said charge-switch nucleotide phosphate is a nucleotide triphosphate (NTP) having a γ-phosphate with a detectable moiety attached thereto.

4. The method according to claim 3, wherein said γ-phosphate with a detectable moiety attached thereto is a γ-phosphate with a fluorophore attached thereto.

5. The method according to claim 1, wherein said intact NP probe is incorporated on a primer strand hybridized to a target nucleic acid using a polymerase, thereby releasing said phosphate detectable moiety.

6. The method according to claim 1, wherein said polymerase is immobilized.

7. The method according to claim 1, wherein said energy field is an electric field.

8. The method according to claim 7, wherein said electric field is a first electric field applied in a transverse direction and a second energy field is applied in an axial direction.

9. The method according to claim 8, wherein said second energy field applied in said axial direction is a pressure field.

10. The method according to claim 1, wherein the charge of said phosphate detectable moiety is greater than said intact NP probe.

11. The method according to claim 1, wherein the charge of said phosphate detectable moiety is less than said intact NP probe.

12. The method according to claim 1, wherein the charge of said phosphate detectable moiety is opposite in sign compared to said intact NP probe.

13. The method according to claim 1, further comprising c) detecting said phosphate detectable moiety.

14. The method according to claim 13, wherein said detection is via a charge coupled device (CCD) camera.

15. The method according to claim 13, wherein said detection is via a dye-impregnated polymeric coating on optical fiber sensor.

16. The method according to claim 13, wherein said detection is via a photodiode.

17. The method according to claim 13, wherein said detection is via a blockade current.

18. A method for identifying an intact charge-switch nucleotide phosphate (NP) probe, said method comprising:

a) contacting a sample comprising said intact charge-switch NP probe with an enzyme to produce a phosphate detectable moiety; and

b) applying an electric field to said sample, wherein said phosphate detectable moiety migrates to an electrode differently than said intact charge-switch NP probe.

19. The method according to claim 18, wherein said electrode is an anode.

20. The method according to claim 18, wherein said electrode is a cathode.

21. The method according to claim 18, wherein either said intact NP probe has a positive molecular charge, or wherein upon cleavage of said phosphate detectable moiety, said phosphate detectable moiety carries a positive charge relative to said intact NP probe.

22. The method according to claim 18, wherein said enzyme is selected from the group consisting of a DNA polymerase, a DNA dependent RNA polymerase, a reverse transcriptase, a phosphodiesterase and a phosphatase.

23. The method according to claim 18, wherein said intact charge-switch NP probe is a member selected from the group consisting of a nucleotide diphosphate, a deoxynucleotide triphosphate (dNTP), and a nucleotide triphosphate (NTP).

24. The method according to claim 23, wherein said deoxynucleotide triphosphate (dNTP) is a member selected from the group consisting of deoxyadenosine triphosphate, deoxycytosine triphosphate, deoxyguanosine triphosphate deoxythymidine triphosphate and deoxyuridine triphosphate.

25. The method according to claim 18, wherein said phosphate detectable moiety is a pyrophosphate with a fluorophore moiety attached thereto.

26. The method according to claim 25, wherein upon cleavage of said pyrophosphate fluorophore moiety, said pyrophosphate fluorophore moiety carries a positive charge relative to said intact NTP probe.

27. The method according to claim 18, wherein said intact NP probe has a positive charge.

28. The method according to claim 18, wherein said intact NP probe has a negative charge.

29. An intact charge-switch nucleotide phosphate (NP) probe, wherein, upon enzymatic cleavage of said intact charge-switch NP probe to produce a phosphate detectable moiety, said phosphate detectable moiety migrates to an electrode, and intact charge-switch NP probe migrates to the other electrode.

30. The intact charge-switch NP probe according to claim 29, wherein either said intact NP probe has a positive molecular charge, or wherein upon cleavage of said phosphate detectable moiety, said phosphate detectable moiety carries a molecular positive charge relative to said intact NP probe.

31. The intact charge-switch NP probe according to claim 29, wherein said charge-switch NP probe is a nucleotide triphosphate (NTP); and wherein said phosphate detectable moiety is a pyrophosphate with a fluorophore moiety attached thereto.

32. The intact charge-switch NP probe according to claim 29, wherein said intact NTP probe has a positive charge.

33. The intact charge-switch NP probe according to claim 31, wherein upon cleavage of said phosphate detectable moiety as a pyrophosphate fluorophore moiety, said pyrophosphate fluorophore moiety carries a positive charge relative to said intact NTP probe.

34. The intact charge-switch NP probe according to claim 29, wherein said NTP probe is a member selected from the group consisting of a deoxynucleotide triphosphate (dNTP), and a nucleotide triphosphate (NTP).

35. The intact charge-switch NP probe according to claim 34, wherein said NTP probe is a deoxynucleotide triphosphate (dNTP).

36. The intact charge-switch NP probe according to claim 35, wherein said deoxynucleotide triphosphate (dNTP) is a member selected from the group consisting of deoxyadenosine triphosphate, deoxycytosine triphosphate, deoxyguanosine triphosphate deoxythymidine triphosphate and deoxyuridine triphosphate.

37. The intact charge-switch NP probe according to claim 34, wherein said nucleotide triphosphate (NTP) is a member selected from the group consisting of adenosine triphosphate, cytosine triphosphate, guanosine triphosphate and uridine triphosphate.

38. The intact charge-switch NP probe according to claim 31, wherein said fluorophore moiety is attached to said terminal phosphate via a linker.

39. The intact charge-switch NP probe according to claim 38, wherein said fluorophore linker is an alkylene group having between about 5 to about 12 carbons.

40. The intact charge-switch NP probe according to claim 38, wherein said linker carries at least one positive charge.

41. The intact charge-switch NP probe according to claim 38 wherein said linker carries at least two positive charges.

42. The intact charge-switch NP probe according to claim 29, wherein at least one of the phosphate moieties of said nucleotide phosphate probe has an ionized oxygen atom with a counter-cation associated therewith.

43. The intact charge-switch NP probe according to claim 29, wherein said counter-cation is a metal ion.

44. The intact charge-switch NP probe according to claim 43, wherein said metal ion is selected from the group consisting of Mg^{++}, Mn^{++}, K^{+} and Na^{+}.

45. A method for sequencing a nucleic acid, said method comprising:

providing a target nucleic acid, a primer strand, a polymerase, and a plurality of NP probes;

mixing said target nucleic acid, said sequencing primer, said polymerase, said plurality of NP probes in a flowcell under conditions permitting target dependent polymerization of said plurality of NP probes, thereby providing a polymerization product; and

separating the polymerization products by an energy field in said flowcell to provide a sequence of said target nucleic acid.

46. The method according to claim **45**, wherein the polymerization of said plurality NP probes produces a plurality of phosphate detectable moieties.

47. The method according to claim **45**, wherein said plurality of NP probes are incorporate`d on said primer strand hybridized to said target nucleic acid using said polymerase, thereby releasing a γ-phosphate with a detectable moiety attached thereto.

48. The method according to claim **45**, wherein said energy field is an electric field.

49. The method according to claim **48**, wherein said electric field is a first electric field applied in the transverse direction and a second electric field applied in the axial direction.

50. A method for sequencing a nucleic acid, said method comprising:

providing a target nucleic acid, a polymerase priming moiety, a polymerase, and a plurality of intact NP probes;

mixing said target nucleic acid, said polymerase priming moiety, said polymerase and said plurality of NP probes under conditions permitting target dependent polymerization of said plurality of NP probes, such conditions which are capable of providing a time sequence of a plurality of phosphate detectable moieties;

separating by charge said plurality of phosphate detectable moieties from said plurality of intact NP probes; and

detecting over time said plurality of phosphate detectable moieties to provide a sequence of said target nucleic acid.

51. The method according to claim 50, wherien said primer moiety is a hairpin loop.

52. The method according to claim 50, wherien said plurality of phosphate detectable moieties independently selected from the group consisting of PPi-Dye, a terminal phosphate fluorophore moiety, a detectable moiety, charged groups, electrically active groups, reporter groups, and combinations thereof.

53. The method according to claim 52, wherien said phosphate fluorophore moiety is a used for a member selected from the group consisting of one-color sequencing, two-color sequencing, three-color sequencing, four-color sequencing and combinations thereof.

54. The method according to claim 50, wherien said polymerase is immobilized in single molecule configuration.